REPORT OF
NATIONAL CANCER INSTITUTE
CLINICAL TRIALS IMPLEMENTATION COMMITTEE

PRESENTED TO THE NCI BOARD OF SCIENTIFIC ADVISORS
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by

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SECTION 1

BACKGROUND

The Clinical Trials Implementation Committee (IC), comprising 27 individuals listed in (Attachment 1), was chaired by Drs. John Glick and Michaele Christian. The IC received its charge (Attachment 2) from Dr. Robert Wittes on 11/26/97. The charge to the IC contained 13 major topics related to overcoming barriers to patient-oriented interventional treatment research which served to focus the subsequent discussions:

18. **Science:** Forging close links with laboratory science and providing needed resources (tissue, technologies).
19. **Development**: Facilitating the development steps necessary to convert interesting molecules (or physicochemical insights) into drugs (or devices) suitable for clinical testing
20. **Peer Review**: Rigorous processes that fairly evaluate proposals for the innovative translational research of small groups and the science and performance of large clinical trial organizations
21. **Consensus Development**: An efficient, inclusive consensus process for phase III trials
22. **Simplification of Trials**: Making clinical experiments as simple as possible consistent with their essential objectives
23. **Streamlining Procedures**: Expediting processes for protocol development and review within both clinical trial organizations and reviewing bodies
24. **Informatic**s: A powerful modern infrastructure for the secure acquisition and transmitting of data
25. **Information Dissemination**: Innovative tools to provide relevant information and educational materials about clinical trials to all who need it and to link with excellent databases of other organizations
26. **Reimbursing Participation**: A flexible financing system that reimburses participants in a realistic manner for what they do (generation of science, accrual of patients, provision of tissue samples, performance of laboratory correlative studies, etc.)
27. **Broadening Access**: Inclusion of participants from all sectors of the health-care system
28. **Forming Partnerships**: Innovative tools to provide relevant information and educational material about clinical trials to all who need it.
29. **Human Subjects Protection**: Optimization of the informed consent process
30. **Training**: institutional and individual training programs to insure a strong clinical research capability in the next generation.

In addition to developing plans and responses to the recommendations of the Clinical Trials Program Review Group (Armitage Committee) (Attachment 3), the IC was asked to address the optimal structure, function and funding of the NCI's Cooperative Group Program. Much of the committee's time and effort was spent responding to this latter charge.

Because the NCI clinical trials program is large and complex and requires the effective collaboration of many constituencies, the IC included both NCI and non-NCI experts drawn from a wide range of backgrounds and representing broad expertise. The IC's initial meetings, therefore, involved considerable discussion and effort to develop a common vision for the clinical trials program and principles which would guide subsequent deliberations. The common functional vision developed by the IC was as follows:

IMPLEMENTATION COMMITTEE VISION OF THE CLINICAL TRIALS SYSTEM

- A system which is open and efficient and flexible enough in terms of funding and structure to shift priorities to pursue the best scientific opportunities and ideas and which accommodates high-risk novel ideas.
- A system which is accessible to all.
- A system that works, that has measurable outcomes for determining success or failure, and that can be realistically implemented within the prevailing health care system.

To carry out its work, the IC met nine times between 12/5/97 and 9/9/98. In addition to these meetings of the committee as a whole, there were additional meetings of 2 subcommittees on Accrual/Access and Idea Generation/Prioritization/Concept Review and 2 Working Groups on Peer Review and Early Clinical Trials. In addition to hearing about new and ongoing initiatives and activities from NCI staff, the IC met with Dr. Robert Comis, Chair of the Cooperative Group Chairs and Dr. H. Samuel Wieand, Chair of the Cooperative Group Statisticians on 5/22, with a group of CCOP Principal Investigators on 6/8 and with all the Cooperative Group Chairs on 7/31.

The IC discussed and modified models and proposals to address perceived needs in the clinical trials system. The resulting Vision, Plans and Pilots of the Implementation Committee constitutes Section 3 of this report. The Committee also discussed each recommendation of the Armitage Committee and reviewed new and ongoing NCI initiatives to address them. The resulting responses to each recommendation are included in Section 4 of this report, Responses to Clinical Trials Program Review Group Recommendations.

One of the benefits of the IC's deliberations was that other groups were stimulated to consider new approaches to many of the issues under discussion. The Cooperative Group Chairs met 4 times to develop new collaborative solutions and to formulate proposals for discussion with the IC. Many of

their proposals have been incorporated into the final plans and pilots proposed by the IC. In addition, a clinical trials summit convened in July by organizers of The March provided many participants in the cancer research enterprise, including patients and advocates, representatives of the pharmaceutical and payer industries, FDA, NCI, researchers and many members of the IC, an additional forum to discuss new opportunities for communication, collaboration and improvements in the cancer clinical trials system. The four pediatric Cooperative Groups announced a plan to merge and have begun discussions and planning to accomplish this.

The IC was challenged by members of the National Cancer Advisory Board and the Board of Scientific Advisors to "think outside the box" and to envision a clinical trials system that was mindful, not only of the need for incremental improvements, but also of the "big picture," the need to reduce the overall burden of cancer in patients. The Committee felt strongly that given the strengths and complexity of the current system, careful piloting and evaluation of new proposals should precede wide-scale implementation. In response, the IC has developed a series of pilots which, if successful, will result in significant changes to the current clinical trials system. The resulting system should facilitate our ability to rapidly address multi-disciplinary scientific questions, including research in treatment, epidemiology, prevention, control of symptoms, and outcomes research evaluating the penetration of new treatments into community practice. It is designed to provide flexibility to identify, prioritize and fund the best ideas and research, whether these be large definitive clinical trials or small developmental clinical trials. It enhances the emphasis on and capacity for translational research. Finally, by laying out a series of pilot projects, the IC has created the expectation that the productivity of the clinical trials system will be re-evaluated and modified through an ongoing process of continuous improvement and a willingness to consider new, more efficient and effective mechanisms for accomplishing the research required to reduce the burden of cancer.

The Report of the Clinical Trials Implementation Committee is divided into five major parts. Section 1 provides background. The Executive Summary (section 2) briefly details key recommendations and changes. Section 3 presents the detailed Vision, Plans and Pilots of the Implementation Committee. Section 4, The Response to the Armitage Committee Recommendations, is organized according to the thirteen major focus topics contained in the charge to the IC and includes a brief description of ongoing or planned NCI initiatives as well as the specific reply and, where appropriate, specific initiatives to address each of the recommendations of the Armitage Committee. Each recommendation is listed, according to the focus topic from the charge which provided the context for its discussion, along with the corresponding answer. Finally, Section 5 contains attachments which provide additional details concerning some of these initiatives. While some of these initiatives are already familiar to the Board of Scientific Advisors (BSA), they are included here for completeness and clarity.

SECTION 2

EXECUTIVE SUMMARY

The Report of the Clinical Trials Program Review Group (Armitage Committee) described the clinical trials system as "an intricate and large research laboratory without walls. This complexity has bred inefficiencies and eroded the ability of the system to generate new ideas to reduce the cancer burden." The Implementation Committee (IC) was mindful of these issues but also of the strengths and productivity of the current system as it began its deliberations. It is noteworthy that 16 of 26 plenary session abstracts at ASCO (62%) between 1993 and 1998 were the product of Cooperative Group research, which clearly has had a tremendous impact on the practice of oncology and the care of patients.

Both before and after the release of the Report of the Clinical Trials Review Group, the NCI initiated a number of new projects to address concerns that had been identified. The IC reviewed each of the Armitage Committee recommendations and relevant NCI projects, policies and procedures. In many cases, the NCI initiatives already in progress appeared to adequately respond to the recommendations. In other cases, the IC recommended new projects and/or modifications in policies or procedures to better address the recommendations. The goal of the IC was not to issue another report but rather to define a concrete plan of action that would effectively implement the recommendations of the Clinical Trials Program Review Group .

The IC was also asked to consider the attributes of an optimal clinical trials system and to propose some plans to bring us closer to that structure. This Executive Summary describes key attributes of the IC's Plan, as well as responses to the major recommendations of the Armitage Committee.

1. Key components of the IC vision included:

A. Focus resources on the best science
B. Efficiency and streamlining
C. Increase accrual and broaden access to patients and physicians
D. **Adequate compensation**

1. Focus resources on the best science

- Open competition among all interested investigators to utilize the national clinical trials system
- Improved decision-making processes: broad-based, independent, and objective peer review of each individual proposal for a large-scale clinical trial, with activation of only those which are outstanding or excellent
- Regularly held national "State-of-the-Science" meetings to bring together the most accomplished scientists in a given disease to identify promising research opportunities with active participation of patients and/or advocates
- Specific peer review criteria for the Cooperative Groups that reward innovation and

translational research in addition to the conduct of large definitive clinical trials

B Efficiency and streamlining

- Major projects to create uniform informatics systems across all NCI supported clinical research projects (and, potentially, industry-sponsored trials as well)
- Reduced administrative and operational redundancy across the clinical trials system
- Greatly expedited protocol development and review
- Mechanisms to permit broad patient access to protocols not previously widely available
- Flexible allocation of funding so that available resources are used efficiently to complete the best studies

C. Increase accrual and broaden access to patients and physicians

- "Open menu" of Phase III trials available to all qualified investigators and patients
- Rapid accrual and completion of important clinical trials
- Development of national educational programs to promote participation and enhance public visibility and understanding of important clinical trials
- Inclusion of physicians in diverse practice settings not currently participating in clinical trials
- Make clinical trials a standard treatment option for all patients with cancer

D. Adequate compensation

- Increased funding for both scientific leadership and the time and effort associated with enrolling and managing patients on clinical studies and assuring data quality
- Enhanced efficiencies to maximize the proportion of funds that reaches investigators and clinicians enrolling patients
- Reimbursement based on actual accruals
- Scientific leadership funds adequate to compensate for the actual time required to lead and manage a clinical study

II. Key components of an open and flexible clinical trials system:

A. An open system of **Idea Generators**: Cooperative Groups, cancer centers, CCOPs, pharmaceutical and biotechnology industry, and independent investigators who develop concepts for Phase III clinical trials

B. **Disease-Specific Concept Review Committees** that perform critical peer review of individual proposals for large trials to ensure concentration of resources on only outstanding or excellent trials. This would allow for the rapid redirection of funds to small developmental trials in that disease or a shift to other diseases when excellent proposals were not forthcoming.

C. Consolidated **Clinical Trials Support Unit(s)** to serve 3 main purposes:

- to consolidate redundant administrative tasks
- to provide linkage of physicians and patients anywhere to the best clinical trials
- to be able to flexibly direct funding for the costs of running clinical trials to wherever the best trials are developed and to the actual sites of patient accrual.

D. A national **Network** of investigators and physicians, including Cooperative Group and non-Group investigators involved in NCI-sponsored clinical research, that can function without artificial boundaries, enrolling patients in high quality trials wherever they may be and regardless of coordinating site.

The IC felt strongly that any broad-scale changes to the present system should be preceded by carefully conducted pilot projects of the components. Major characteristics of the pilots are:

III. Pilot projects to establish and test key components:

A. Disease-specific Concept Review Committees

- These will carry out independent peer review of proposed Phase III studies and will approve only those of Outstanding or Excellent merit according to specified criteria
- Membership will be rotating, based on nominations from all stakeholders, and appointed by the NCI Director with input from the Board of Scientific Advisors
- These committees will be constituted specifically to have no more than 1/3 representation from the Cooperative Groups, no more than 1/3 representation from NCI, and will include community physicians, basic scientists, patients and/or advocates, and others
- The initial pilot will concentrate on genitourinary (GU) and lung cancers. If successful, it will be extended to gastrointestinal cancers and adult leukemias.

B. State-of-the-Science Meetings

- Regularly scheduled national forums to identify new research opportunities in specific cancers, or gaps in research portfolios. These will be similar to but larger in scope than prior NCI/CTEP strategy meetings and will be broadly representative of the cancer research enterprise, including patients and/or advocates
- Outcomes of these meetings will be broadcast widely and made easily accessible to all investigators and the public, and should serve as a stimulus to new proposals for trials
- In the initial pilot, NCI will organize these meetings in GU and lung cancer, and a committee of the Cooperative Group chairs will organize them in gastrointestinal cancers and leukemia

C. Clinical Trials Support Unit (CTSU)

Will be established in GU, lung, breast, and gastrointestinal cancers and adult leukemias initially, to take on the following tasks on a pilot basis:

- to consolidate redundant administrative tasks
    - management of credentialing, drug distribution, IRB tracking, audit management, forms development, performance evaluation and quality assurance, etc.
- to provide linkage of physicians and patients anywhere to the best clinical trials
    - registration of patients to national phase III trials sponsored by Groups or centers, other than those with which the treating physician is affiliated (cross-Group registration)
    - distribution of protocol information and education to support this function
- to direct funds for support of clinical trials to the best trials and to sites of actual

accrual

- instead of clinical trials funding being awarded entirely to individual entities on the basis of anticipated future performance, part of the funds will go into a central resource from which they can be disbursed according to the ongoing actual levels of scientific leadership and patient accrual with provisions for front-loaded funding based on historical accrual to provide a stable research infrastructure.

D. Network of investigators.

In the pilot, this will be limited to current credentialed investigators of the Groups, with the intent to expand beyond this to new participants in the future.

IV. Enhanced efficiency

- Major informatics initiatives already underway, including electronic protocol development, submission and management will support the above pilot projects
- Protocol development and NCI review will be dramatically streamlined
- 60 day maximum from concept approval to protocol approval
- No NCI review for DSMB approved non-IND Phase III protocol amendments

V. Enhanced Peer Review

The NCI's Clinical Trials Cooperative Group Program was designed to be a standing apparatus for the conduct of multi-institutional clinical trials. While a valuable feature, this poses challenges in ensuring that the investigational activities of each Group reflect the most important current scientific opportunities. The IC sought to define rigorous processes that fairly evaluate scientific proposals while reducing the burden of application on investigators and the consequent diversion from research activities. Recommendations to enhance the evaluation of Group scientific activities and to promote the retention of meritorious participants include:

- Encouraging competition of ideas for individual Phase III studies through the proposed concept review process, broadened to include non-NCI experts and patient advocates, and informed by State-of-the Science Meetings that identify new areas of opportunity, as described above.
- Soliciting proposals for individual hypothesis-driven translational studies utilizing Group clinical resources, with study-section evaluation by the newly established Clinical Oncology Special Emphasis Panel of the Center for Scientific Review, NIH. Proposals for translational studies would compete against others in the Research Project Grant (RPG) pool, with applications accepted three times per year.
- Continued periodic review by NCI study section (Subcommittee H-CCIRC) of Group research strategies, accomplishments and plans, with renewed emphasis on evaluation of Group developmental research preparatory to Phase III clinical trials and continued emphasis on Phase III plans and performance.
- The maximum award period for groups and committees judged as excellent to outstanding will be lengthened to six years. Interim peer review at three years will be Mandated for disease and modality committees judged less than excellent by Subcommittee H. Re-review will focus on deficiencies identified in the prior review; if insufficient progress is identified, the committee

in question will be phased out.

- Simplifying and streamlining the application process to improve the quality of applications and review, and to reduce the downtime associated with submission. Specific measures might include utilizing page limits, standard formats for institutions and committees, tabular displays of information, and electronic facilitation of the application process where possible. Application formats for committees might include an abstract; a concise outline of each active and planned protocol; bullet presentation of accomplishments; and a timeline in schematic fashion indicating research strategy and development plans.
- Supporting innovative research within the Group context through two mechanisms, the R-01 and R-21 peer-reviewed application, and a newly established developmental fund within the Group Chairman's award. This latter mechanism is intended to allow the Group to pursue its translational research agenda by providing seed money for lab/clinical correlative studies in order to acquire pilot data upon which to base subsequent RPG applications. This feature would be analogous to developmental funds included in cancer center core grants. Group policies and procedures for internal peer review of the uses of developmental funds would be required, and utilization of these funds would be evaluated at the subsequent Subcommittee H review of the Group.
- Establishing equitable and adequate reimbursement mechanisms based on actual accrual for all Groups, with up-front payments by the Group Operations Office to accrual sites in order to promote stability of data management staff. Groups will have the option of applying for individual institutional U-10 awards for support of Group scientific contributions by institutional personnel and for support of data management during follow-up. In addition, CCOPs will continue to hold individual U-10s based on accrual and scientific contributions.
- Funding Group applications at full peer review recommended levels will ensure adequate salary support for time and effort spent on Group-related scientific activities. Additionally, a mechanism for providing supplementary funds for leadership of large Phase III trials which require augmented levels of effort should be established.

VI. Other Recommendations of the Implementation Committee

- The NCI should hold an Information Technology Fair or Conference to make the cancer research community aware of its initiatives in information technology in order to avoid duplicative efforts.
- The NCI should take an active role in interacting with Institutional Review Boards (IRBs) and participating in educational efforts directed toward IRBs.
- The NCI should make its efforts to pilot and develop a national IRB a high priority.
- The NCI should enlist the assistance of advocacy groups in its efforts to develop a central IRB and to promote the utilization of the simplified informed consent templates.
- The NCI should conduct a study of the incremental costs associated with Phase I trials and that NCI should continue its vigorous attempts to secure coverage for these by payer organizations.

VII. Metrics for evaluation of these projects:

The IC stressed the importance of developing plans for evaluating the success or pinpointing the problems with each of these projects, for determining if and when they should be expanded. Some reasonable approaches to evaluation are described in Section 3, however, the IC recommended that a professional consultant be retained early in the process to help develop an effective assessment plan.

The Implementation Committee believes that the measures described in this report, combined with a firm commitment to continuous improvement, will result in substantial strengthening of the national clinical trials program. These efforts and a sustained willingness to consider new, more efficient and effective mechanisms for accomplishing the research, will lead to a significant reduction in inbred inefficiencies and stimulate the system to generate the new ideas required to reduce the cancer burden

EXECUTIVE SUMMARY OF THE IMPLEMENTATION COMMITTEE'S RESPONSE TO THE MAJOR RECOMMENDATIONS OF NCI'S CLINICAL TRIALS PROGRAM REVIEW GROUP

Below are summaries of the Implementation Committee's response to the 11 major recommendations of the Clinical Trials Program Review Group**.** Complete answers to all 48 recommendations can be found in Section 4 of this report.

(The recommendations of the Clinical Trials Review Group are in bold-face type and are followed by the Implementation Committee's response.)

A patient-oriented clinical cancer research and training study section in the NIH Division of Research Grants is critical.

The NCI has worked with the Center for Scientific Research, NIH to establish the Clinical Oncology Special Emphasis Panel which will review patient-oriented clinical cancer research grants (R01s and R21s) and fellowship grants (F32s). The NCI currently reviews the National Research Service Awards and career development awards (T and K series).

The NCI should increase funding for cooperative groups to fully recommended levels.

The NCI is committed to the concept that funded Cooperative Groups should be supported at full peer review recommended levels. The NCI has begun planning for this with initial emphasis on providing consistent reimbursement for accrual across the Cooperative Group network. Attainment of full peer review recommended levels is expected to occur over a period of 3-4 years. This commitment will require an approximate doubling of the current level of support.

In designing clinical trials, data collection should be reduced so that only data pertinent to the study endpoints and patient safety are accrued. In addition, NCI-funded efforts should include some large, uncomplicated trials in common cancers with minimal data requirements and accrual goals large enough to establish treatment differences definitively.

The NCI has begun a joint initiative with the FDA, the pharmaceutical industry, and clinical investigators to develop common definitions of endpoints along with novel endpoints and clinical trial designs. Common case report forms and data elements are being jointly developed by the NCI and the Cooperative Groups in breast, colon, lung, prostate, and gynecological cancers. Common post-randomization forms have already been jointly developed and are being pilot tested in a new NCI initiative (the Expanded Participation Project described in Attachment 9). These initiatives coupled with broadened access and increased accrual to trials that are major objectives of the Pilot Projects (described previously for lung, genitourinary, breast, and gastrointestinal cancer and leukemia) should facilitate the performance of large, simple trials when such trials are appropriate. However, NCI's clinical trials system must also be capable of doing more complex, data-intensive trials when required by the scientific question being tested, for example, studies involving laboratory correlates, quality of life, or economic outcomes.

Uniformity of data collection for patients on clinical trials in cooperative groups and cancer centers is essential.

In addition to the data reduction initiative mentioned above and the development, with the Cooperative Groups, of common case report forms and data elements, the NCI has implemented a common toxicity reporting system, a clinical data update system, and a simplified adverse event reporting system. These initiatives, when completed, should provide the framework for a uniform and simplified system of clinical trials data collection and reporting for Cooperative Groups and Cancer Centers.

NCI should enlist the clinical trials and patient advocate communities as well as the pharmaceutical industry to work with the Food and Drug Administration to develop uniform standards and reporting requirements for everyone involved in oncology clinical trials (e.g., pharmaceutical industry, academia, cooperative groups, cancer centers).

The NCI has met with the FDA and representatives from the pharmaceutical industry to initiate the Common Data Elements and Data Reduction initiatives. Each have expressed high interest in both projects and are interested in working with the NCI on these. NCI will form working groups to address these two initiatives. In addition to representatives from the NCI, the FDA, and industry, clinical investigators, statisticians, and patient advocates will be included in each working group.

In order to create and prioritize the best new ideas in cancer treatment and prevention, the NCI-funded Cooperative Groups and Cancer Centers should be provided with the means to access all relevant electronic databases, and should be primary participants in the development and testing of the new NCI informatics system.

Representatives from the Cooperative Groups and Cancer Centers have been active participants in the development and testing of the different components of the NCI informatics enterprise system. This includes the clinical data update system, the common toxicity criteria system, the adverse event reporting system, and the audit information system. In addition, Cooperative Group representatives are active collaborators in the development of common case report forms and the

development and testing of common post-randomization forms. Clinicians and statisticians from the Cooperative Groups and Cancer Centers have been invited to participate on the working groups to develop common data elements and to look at reducing the amount of data collected in clinical trials.

For phase III and phase II studies, not involving new agents, the Cancer Therapy Evaluation Program of the Division of Cancer Treatment and Diagnosis should approve study concepts and collaboratively establish research priorities, and its authority should otherwise be limited to regulatory and safety issues and prevention of unnecessary duplication.

All Cooperative Group phase III trials will undergo concept review (except those funded entirely by industry for conduct in a single Group). A new mechanism of disease-specific Concept Review Committees will be piloted in genitourinary and lung cancers, other sites will continue with current CTEP concept review. Standardized forms will be developed for concept review to insure that sufficient information is provided regarding rationale, importance, statistical design, etc. Following concept approval, protocol assembly will be done jointly between the principal investigator and CTEP using electronic means. The CTEP Protocol Coordinator will be responsible for consistency and completeness of the document. Further formal protocol review will not be necessary, unless regulatory or safety concerns cannot be resolved. For phase II trials not involving new agents, review will be advisory except as stated for regulatory, safety or duplication.

Representatives of patients and high-risk communities must be integrated into the clinical trials decision-making process.

As the decision-making process is reconfigured, consumer representatives will be included. This inclusion needs to take place at the Cooperative Group decision-making level as well. Most Groups have already moved to assure inclusion of consumers. The disease-specific Concept Review Committees that are to be piloted in several diseases will include patient representatives.

Therapeutic trials conducted through the Community Clinical Oncology Program should be transferred to the Division of Cancer Treatment and Diagnosis. Cancer prevention studies conducted across the NCI clinical trials system should be the responsibility of a newly configured Division of Cancer Prevention.

Oversight of clinical treatment trials has been and will continue to be the responsibility of CTEP, DCTD. Thus, protocol review for treatment trials in which the CCOPs participate has been and will continue to be the responsibility of CTEP, DCTD. Prevention and control research, including resource allocation, protocol design and review through the CCOP Network is the responsibility of the new Division of Cancer Prevention. In order to make this clear to investigators, the NCI intends to reconfigure its internal operations so as to facilitate interactions. Regardless of the administrative location of treatment and prevention trials in the CCOPs, the NCI will simplify its procedures for letters of intent, protocol submissions, and data reporting, with the goal of making its internal operations more transparent to the investigator.

To insure the success of cancer clinical trials, NCI should increase training opportunities for

new and mid-career investigators.

The NCI has developed new award mechanisms for both new and mid-career investigators. For junior faculty, two types of awards are proposed. Prolongation of KO8 awards should allow basic scientists more time to become fully independent investigators. For clinical researchers, a new K22 award is proposed for MD's. As for mid-career investigators, the NCI is in the process of developing a career award mechanism (the K24) that will provide established clinical scientists 50% salary support as protected time to conduct research or engage in any activities directly related to research (e.g., mentoring). A series of transition awards is also planned to optimize the chances that previously trained investigators will succeed in establishing themselves as independent investigators.

NCI should develop strategies, including necessary databases, to convince payers that clinical trials are the preferred way to manage cancer patients, that they represent a better standard of care, and ultimately result in decreased costs.

A new Office of Clinical Research Promotion has been created in the Office of the Deputy Director for Extramural Science to address these and other issues. Several initiatives are ongoing with the payer community to assure coverage for clinical trials including negotiations between the NIH and the American Association of Health Plans. Economic analyses have been undertaken to accurately measure the incremental costs of clinical trials in comparison to standard therapy. Three single institution studies have been completed and manuscripts are being prepared for publication. NCI is also working on various strategies of educating the public about the importance of clinical research in cancer including the initiation of a new clinical trials web site and developing clinical trials training sessions at national meetings such as ASCO, ONS, and NMA.

The Implementation Committee believes that the pilots, initiatives and responses to the Clinical Trials Program Review Group Report recommendations contained in this report are consistent with its stated vision: A system which is open and efficient and flexible enough in terms of funding and structure to shift priorities to pursue the best scientific opportunities and ideas and which accommodates high-risk novel ideas. A system which is accessible to all. A system that works, that has measurable outcomes for determining success or failure, and that can be realistically implemented within the prevailing health care system.

The initiatives and pilots described in this report should be carried out over the next several years with regular reports to the Board of Scientific Advisors regarding progress, evaluation and plans for further implementation.

Section 3
Clinical Trials Implementation Committee
Vision, Plans and Pilots

SECTION 4

CLINICAL TRIALS IMPLEMENTATION COMMITTEE
RESPONSES TO RECOMMENDATIONS OF
NCI's CLINICAL TRIALS PROGRAM REVIEW GROUP (ARMITAGE COMMITTEE)

This section is organized according to eleven of the major focus topics included in the charge to the committee (Attachment 2). The bordered single box following each major topic describes ongoing or planned NCI initiatives. Then follows the specific reply and/or appropriate initiatives to address each of the recommendations of the Clinical Trials Program Review Group. The left column lists the recommendations of the Clinical Trials Program Review Group and the right column contains the Implementation Committee (IC) response. (NOTE: the numbers associated with the questions are not in numerical order and do not refer to specific location within the Clinical Trials Program Review Group report. They were used to track the questions.)

I. Science: Optimizing the integration of translational science into the clinical trials program (Cooperative Groups, Cancer Centers, grantees) and forging close links with laboratory science and providing needed resources (tissue, technologies).

- **resources (technology, tissues, etc.)**
- **investigators**
- **identification of ideas**
  - **-early clinical trials**
  - **-late clinical trials**
- **process for rapid movement of best ideas**

The IC Pilots & Plans contain a number of changes which will enhance the identification of best ideas in both the early and late clinical trials programs. See attachment 4. These include inclusive, disease-specific State-of-the-Science Meetings, Disease-Specific Concept Review Committees, and greater availability of developmental funds for correlative laboratory studies both in the Cooperative Groups and in the Early Clinical Trials Cooperative Agreements.

NCI is developing processes for facilitating movement of promising ideas from preclinical evaluation into "proof of concept" clinical trials and then more definitive testing. These include the RAID Program (attachment 5) and planned modifications of the UO1s for early drug development which are under discussion (Attachment 4).

Resources for enhancing translational research include available Tissue Banks (attachment 6), Program Announcement for Correlative Studies in Clinical Trials utilizing specimens from the tissue banks (attachment 7) and implementation of individual Group Chairs' Developmental Funds.

Armitage Recommendation		Implementation Committee Response
10.	The NCI-designated cancer centers should be encouraged to participate in cooperative group research. In addition, participation in cooperative group studies should be viewed favorably in the cancer center review process.	**The Cancer Centers will be encouraged to participate in Cooperative Group trials and language to that effect will be incorporated into the revised Cancer Center Guidelines.**
40.	For Phase III and Phase II studies not involving new agents CTEP is to approve study concepts and collaboratively establish research priorities, and its authority should be otherwise limited to regulatory and safety issues and prevention of unnecessary duplication.	All Cooperative Group Phase III trials (except those funded entirely by industry for conduct in a single group) will undergo concept review. A new mechanism of disease-specific Concept Review Committees will be piloted in genitourinary and lung cancers, while other sites will continue with current CTEP concept review. Standardized forms will be developed for concept review to insure that sufficient information is provided regarding rationale, importance, statistical design, etc. Following concept approval, protocol assembly will be joint and electronic with PI and CTEP. The CTEP Protocol Coordinator will be responsible for review for consistency and completeness of the document. A detailed, formal protocol review in addition to concept review will not be necessary, unless regulatory or safety concerns cannot be resolved. For Phase II trials not involving new agents, review will be advisory except as stated for regulatory issues, safety or duplication.
36.	The cooperative group grants should include a salary commitment to the responsible committee chairs to ensure that time and effort is matched by salary support in the planning, implementation, and review of trials.	We agree with this recommendation and believe that it is a high priority to provide the funding to accomplish this goal. NCI plans to move to full funding of Cooperative Groups through annual budget increases over the next 3-4 years. Initial emphasis will be on providing minimum $1,500 support for all patient accruals across the system and on providing Leadership Funds for intergroup clinical trials.

II. Peer Review: Rigorous processes that fairly evaluate proposals for the innovative translational research of small groups and the science and performance of large clinical trial organizations

- **DRG**
- **CCIRC**
- **Concept Review**
- **Review Criteria**

NIH plans for a Clinical Oncology Special Emphasis Panel in the Center for Scientific Review (formerly DRG) to be implemented for the review cycle beginning 10/1/98 are detailed in attachment 8. A Program Announcement encouraging translational studies linked to Group trials is to be published. Resulting applications will be reviewed three times annually in the new Study Section.

In addition, the IC Plans & Pilots (attachment 4) contains a description of proposed revisions to the process of Peer Review of Cooperative Groups, including changes in the period of award, grant application and review criteria. The science of each proposedPhase III trial will also be reviewed in the Disease-Specific Concept Review Committees.

Armitage Recommendation	Implementation Committee Response
45. Given the fact that the current Cooperative Groups are 17 to 41 years old and each has successfully completed multiple competitive renewal applications, if legislatively possible, the interval for funding established Cooperative Groups should be lengthened from the current five years to eight to ten years. New Groups, for which there is no previous track record, should be limited to the current interval and be granted longer funding durations after successfully completing two competitive renewal applications.	A 6 year maximum award period for the Group as a whole and all committees rated excellent or better is recommended. A 3 year award period is recommended for committees rated less than excellent, followed by CCIRC re-review of the performance of that committee

III. Prioritization/Consensus Development: An efficient, inclusive consensus process for phase III trials to facilitate efficient evaluation of the best ideas

- **how inclusive (geography, people, etc.)**
- **how to elicit**
- **areas of emphasis**
- **Process:**
  - **committee composition/selections**
  - **decision-making**
  - **use of virtual meetings**

The IC Vision, Plans & Pilots (Section 3) includes restructuring current scientific strategy meetings, which predominantly involve the Cooperative Groups, with pilots of two approaches. 1. State-of-the-Science Meetings in lung and genitourinary cancers will include basic scientists, cancer center and SPORE investigators, statisticians, patients and advocates and other relevant participants, including those from other disciplines, i.e., prevention. 2. In gastrointestinal cancers and leukemia, the Group Chairs will organize the State-of-the-Science Meetings and lead the consensus development process preparatory to intergroup trials. Broader and more open access to identification and generation of large important clinical trials is planned.

Prioritization will be accomplished through the Disease-Specific Concept Review Committees (details in attachment 4). Modern conferencing technology (video- and teleconferencing and dedicated web sites) will be used to facilitate communication.

IV. Streamlining and Efficiency: Expediting processes for protocol development and review within both clinical trial organizations and reviewing bodies

- **simple process**
- **technology solutions**
- **delegation of authority**
- **parallel processes**
- **CTEP protocol coordinator**

A number of projects and initiatives are underway at the NCI to facilitate streamlining, including:

- Electronic document management with parallel, rather than serial review of protocols and amendments in CTEP.
- Electronic protocol submission pilot with Pediatric Oncology Group
- Electronic Letter of Intent Submission and review
- Increased emphasis on simplification of eligibility criteria and other parameters in protocol review

Armitage Recommendation		Implementation Committee Response
37.	The Cooperative Groups and CTEP need well-defined time lines for protocol development, approval, and activation with clearly stated positive and negative consequences of not meeting those time lines.	For Phase III trials, CTEP will assign a protocol coordinator for all approved concepts. This person will be responsible for coordinating co-development of the protocol between relevant CTEP branches and the PI and/or Group protocol coordinator. A 60 day maximum from concept approval to protocol approval is the goal. CTEP will track and report performance in this area, along with progress on other projects and operations to the BSA.

20.	Rapid protocol development is critical to the ability to implement new ideas and concepts in an expeditious fashion. Groups should develop a common algorithm for protocol development in order to minimize the time necessary to develop and obtain a letter of intent or concept to NCI for consideration and review.	A 60 day maximum from concept approval to protocol approval is expected. CTEP will track and report performance in this area, along with progress on other projects and operations**.**
41.	For studies involving investigational new agents, CTEP should retain its current legislated authority and responsibility, in partnership with industry and theCooperative Groups.	CTEP will continue its current legislated authority in partnership with industry and the Cooperative Groups for CTEP IND sponsored studies.
42.	For most prevention and control studies, the Cooperative Groups should be provided with the authority to establish priorities and conduct studies. For large-scale cancer prevention and controlled Phase III studies, DCPC (or, preferably, a combined DCTDC/DCPC review process) should actively participate in concept approval and priority setting	The Research Bases for the CCOPs are the Cooperative Groups along with three cancer centers. These Research Bases develop the cancer prevention and control concepts and protocols that are used in the CCOP Clinical Trials Network including Cooperative Group members and affiliates. Large-scale phase III studies (BCPT, PCPT, STAR) require a very large administrative supplement to adequately fund. Thus, all large-scale prevention clinical trials undergo external peer review by an ad hoc review committee and are awarded as peer-reviewed supplements to the CCOP Research Base Award. Because the science and design of prevention clinical trials are less mature than for cancer treatment trials, the Division of Cancer Prevention (DCP) currently reviews all concepts and protocols to evaluate the scientific rationale and design and the appropriateness for the CCOP Network. DCP is assessing the roster of prevention and control clinical trials to determine if there is a category of studies for which a concept review would be advisory only (similar to the treatment studies with a sample size of less than one hundred and no IND required for which CTEP review traditionally has been advisory). The oversight and management of trials in prevention and cancer control will be addressed directly by Implementation Groups dealing with the recommendations from the Bresnick and Abrams Reports.

Armitage Recommendation		Implementation Committee Response
43.	Amendments and addenda to the trials should become the full responsibility of the group conducting the study rather than the ultimate control residing within NCI.	For administrative amendments - no prior NCI approval will be required. For scientific amendments (which change trial concept, design, accrual target, etc.) to CTEP IND sponsored trials, CTEP review is required as IND sponsor.

	Amendments should be filed with, but not require the approval of, NCI.	For scientific amendments (which change trial concept, design, accrual target, etc.) to studies not involving a CTEP IND, CTEP will accept and file amendments approved by the study's Data Safety and Monitoring Board (DSMB) without further review. CTEP will institute electronic amendment review to reduce the current average 15 day turnaround.
44.	The separate protocol review processes of DCTD and DCPC should be combined to avoid the delays, contradictions, and perplexity of the existing mechanism.	A common set of procedures governs the review process for DCTD and DCP. Each Division utilizes the same protocol checklist and format in protocol review. All protocols are sent to the CTEP Protocol Information Office (PIO) and triaged to the appropriate Division for review. When a study involves both treatment and cancer control, it is assigned to the appropriate Division based upon its primary purpose with a reviewer from the other Division if deemed appropriate. For example, a lung cancer treatment study with quality of life endpoints will be assigned to CTEP with a CORB reviewer, while a prevention trial of second lung cancer in stage I resected patients will be assigned to DCP with a CTEP lung specialist as a reviewer. The DCP review process now takes an average of 10 weeks from receipt by the Protocol Information Office and efforts are underway to further reduce this time-frame. Because the scope of prevention and control research is broad, DCP draws on ad hoc reviewers within the NIH to provide protocol specific expertise (nutritional agents, genetic issues, etc) and accommodations to the ad hoc reviewers' schedules can occasionally prolong the review process. DCP and DCTD are working together on new informatics initiatives intended to further streamline the protocol review process.

V. Broadening Access/Accrual: Inclusion of participants from all sectors of the health-care system

- **academia**
- **community**
- **HMO/MCO**
- **demographic**
- **ethnic**

The IC Vision, Plan & Pilots (Section 3) provide open access to State-of-the-Science Meetings, concept submission and Disease-Specific Concept Review Committees as well as open enrollment on Phase III trials. This open access will include both academic and community investigators, as well as explicit participation of basic scientists and patients and advocates. The IC envisions that a broader range of scientific questions and interests can be addressed (see answer to #6 below).

The Expanded Participation Project (attachment 9), developed in part in response to NCI Listens at ASCO 1997 is a pilot project designed to attract new physician participants in the clinical trials program through provision of an open menu of Phase III trials across Cooperative Groups, employing simplified common case report forms for follow-up data accessed through a web-based system and a single source of contact, a Clinical Trials Management Unit, for information requests, patient registration, and data reporting.

Activities of the Office of Clinical Research Promotion will facilitate these outreach efforts.

The development of electronic connections, common data elements and common case report forms through NCI informatics initiatives (attachment 11) will also be critical to the success of these efforts.

Armitage Recommendation	Implementation Committee Response
6. The NCI should continue to improve its efforts to recruit and retain minorities, underserved populations and the elderly in clinical trials and to tailor its approaches to address linguistic and cultural differences.	CTEP has initiated an informatics project, the Physician Communication Module, with Howard University Cancer Center. This project will develop electronic tools to inform physicians about clinical trials suitable for individual patients in their practices and provide electronic materials about protocols for the physicians and patients. Culturally appropriate educational materials will be developed as part of this project. A Program Announcement is being developed in collaboration with National Institute on Aging to fund hypothesis driven studies in elderly populations within the Cooperative Groups In addition, procedures for cross-group registration of patients will allow accrual beyond the demographic constraints of individual Groups. The concept review process will facilitate submission of concepts by a broader group of investigators and, together, these changes will allow entirely new types of questions to be addressed. More focused marketing of specific clinical trials will be possible. In addition, the communication and educational advancements inherent in the PDQ Redesign initiative (Clinical Trials Information System -attachment 10) will facilitate and enhance these efforts.

VI. Reimbursing Participation: A flexible financing system that reimburses participants in a realistic manner for what they do (generation of science, accrual of patients, provision of tissue samples, performance of laboratory correlative studies, etc.)

- **realistic for character and level of effort (intensity)**
- **flexible**
- **how to reward/reimburse the activities that need to get done**
  - **academia**
  - **community**
  - **industry**
- **what kind of structure does that require**

The IC Vision, Plans & Pilots (Section 3) contains a proposal to equalize minimal funding at $1500 per patient across the Cooperative Group system. In addition, the plans call for increased Leadership funds for scientific leadership of Phase III and intergroup trials. The plan is conducive to flexible redistribution of Phase III funds from areas that are less active to areas of more promising scientific opportunity. The plan also establishes the Group Chair's Developmental Fund to allow dollars to be directed to the most promising scientific priorities of the group.

NCI is committed to providing fair compensation for the work performed and is undertaking a study to define the costs to the physicians and health care providers of participation in clinical trials as a basis for determining future funding levels.

Armitage Recommendation		Implementation Committee Response
7.	The NCI should increase funding to Cooperative Groups to fully recommended levels to ensure adequate patient accrual.	The NCI is committed to the concept that funded Cooperative Groups should be supported at full peer-review recommended levels. Since a number of Cooperative Groups are currently funded significantly below this level, the dollar amount required to bring the current cooperative group system to recommended levels will likely exceed available funds for any particular fiscal year. Thus the necessary restitution is expected to occur over a period of 3-4 years. The NCI has already begun planning for this in its budget projections with initial emphasis on providing consistent reimbursement for accrual across the system. Implementation will require a near doubling of the dollar investment.
27.	When intergroup studies are judged necessary, extra funds should be provided by NCI to the coordinating group to cover additional expenses. This is particularly critical during registration and evaluation, but also is needed for patients in follow up.	In the transition to Clinical Trials Support Units and uniform informatics, many of the costs and burdens associated with running intergroups will be reduced. In the meantime, additional funding will be awarded for leadership of these trials
29.	Systems for awarding proper credit and funding to each institution participating in an intergroup study must be developed.	Peer Review criteria will evaluate and appropriately reward excellence of logistical support systems and group accrual in addition to scientific content, innovation and leadership. NCI will establish a per-patient method of funding for all participants with front-loaded funding to insure stability for extended periods.
47.	Future funding for cooperative group operations should be based on the costs of performing as a headquarters office, and proportional to CCOP membership.	NCI agrees that the funding of operations offices should take extent of CCOP membership into consideration. This question will also be addressed by the Prevention Report Implementation committee
48.	Therapeutic trials conducted through the CCOP mechanism should be transferred to the Division of Cancer Treatment, Diagnosis, and Centers. Cancer prevention studies conducted across the NCI clinical trials system should be the responsibility of a newly configured Division of Cancer Prevention and Control.	The IC discussed this and concluded that therapeutic trials are currently administered by CTEP. Decision making, and protocol review for treatment trials in which the CCOPs participate has always been the responsibility of CTEP. Prevention and control research including resource allocation, protocol design, and review through the CCOP Network is the responsibility of the new Division of Cancer Prevention (DCP). Whatever the organizational location of treatment and prevention trials in the CCOPs, the NCI will continue to simplify and harmonize its procedures for letters of intent, protocol submissions, and data reporting, with the goal of making its internal operations more transparent to the investigator.

VII. Simplification of Trials: Making clinical experiments as simple as possible consistent with their essential objectives

- **eligibility**
- **design**
- **baseline studies**
- **interval tests**
- **endpoints**

CTEP sponsored trials of promising agents in patients with abnormal organ function (hepatic and renal function, prior chemotherapy treatment) and in special populations, such as the elderly, may facilitate simplification and relaxation of eligibility requirements by providing knowledge about the disposition, effects and safety of drugs in these populations.

The international collaboration to define uniform response criteria (RECIST) (attachment 12) will also contribute to a simplification and harmonization of endpoints and interval tests.

Armitage Recommendation		Implementation Committee Response
9.	Entry criteria for all studies need to be simplified and broadened. A range, rather than an absolute set, of parameters should be considered.	Eligibility for Phase III trials should be broadened to reflect the general patient population and the preparatory work in populations with abnormal organ function, poorer performance status, and the elderly, etc., should be done in Phase II to allow this to be done safely. CTEP will increase its sponsorship of these preliminary trials.

8.	In designing clinical trials, data collection should be reduced so that only data pertinent to the study endpoints and patient safety are accrued. In addition, NCI-funded efforts should include some large, uncomplicated trials in common cancers with minimal data requirements and accrual goals large enough to establish treatment differences definitively.	A robust clinical trials system will require some balance between large simple trials and more complex ones. Data collection for all trials should be minimized to the greatest extent possible, consistent with the question being addressed. NCI is engaged in a "Data Reduction Initiative" with FDA and the pharmaceutical industry. Cooperative Group investigators will also be active participants. It is understood that study endpoints may include laboratory correlative studies and other correlations beyond the traditional survival, time to progression, response, etc.

16.	All Groups and cancer centers should use the same protocol guidelines so that each critical element in a format is the same across protocols. This will allow clinical research associates, who deal with the protocols on a daily basis, to move easily and efficiently from protocol to protocol, regardless of the group of origin.	Systems for Electronic Protocol Development are being collaboratively developed as part of the informatics initiative. The early development stages of this system are described in attachment 11)
17.	The eligibility criteria for all cancer clinical trials should be simplified in order to require minimal input at the time of registration of individuals, and to substantially reduce the workload for the individual conducting the registration..	Eligibility criteria will differ based on the phase of study and amount of available data on drug toxicity and disposition in varied settings. The simplest eligibility criteria consistent with available data and the objectives of the study should be employed. The use of Common Data Elements (in development) should simplify and further reduce the burden of registration.

Armitage Recommendation		Implementation Committee Response
18.	Study endpoints should be standardized. Common endpoints would render protocols simpler and more uniform. This could result in substantial cost savings by reducing the number of study parameters necessary to document surrogate endpoints, such as partial and complete response to treatment.	NCI plans a joint initiative with FDA, industry and clinical investigators to develop common definitions of endpoints and novel endpoints and trial designs Common Data Elements and Common Case Report Forms should facilitate this effort. Common toxicity reporting has already been implemented. In the Expanded Participation Project described in Attachment 9, the NCI and Cooperative Group statisticians have collaborated in the development of common follow-up report forms for ongoing Phase III trials in common disease. An international committee has been working on common response criteria for the past 2 years. The final RECIST document is nearing completion (Attachment 12 is current draft). These initiatives should all contribute to widespread use of more

		standardized endpoints.
19.	To limit the cost of clinical trials, NCI and Groups conducting trials should reduce the number of study parameters required in any given trial to only those that bear on patient safety and documentation of endpoints.	See answers to #8, 17 and 18 above. Common Case Report Forms/Common Data Elements and uniform informatics will also limit costs.
21.	All Cooperative Groups and cancer centers should use the same common data collection forms. This would optimize the ability to exchange data in intergroup studies. Flow sheet information should be captured on single patient encounter forms to allow the computerization of data which could then be sent electronically to the appropriate statistical center.	Common Data Elements and Common Case Report Forms informatics projects described in Attachment 11 and in the answer to #15 above address this recommendation. Group statisticians are developing common case report forms in breast, colon, lung, prostate and gynecological cancers
22.	Common toxicity criteria should be developed in order to overcome the complexity of toxicity tables that now exist. This would allow for uniform toxicity criteria across all studies and would provide comparability across the system.	DONE.
ARMITAGE RECOMMENDATION		**IMPLEMENTATION COMMITTEE RESPONSE**
23.	Common biostatistical principles should be developed for use in evaluating data such as endpoints and sample size. There is considerable variation in statistical sections from one group to another concerning such issues as sample size, design considerations such as stratification, early stopping rules, and handling subset analyses.	This would be facilitated by Common Endpoints Initiative, however, innovation and creativity in this area should be preserved and encouraged
24.	Common and simplified adverse drug reaction and adverse event reaction reporting is essential to creating a system that protects clinical trial participants.	DONE.
26.	The decision to conduct an intergroup trial should be based on investigator initiative. When conducted, the intergroup trials should be harmonized and simplified.	Intergroup development and administration have been addressed in the proposals of the Group Chairs. The Concept Review/Open Menu approach will replace intergroups if successful. Uniform informatics and common forms will facilitate harmonization
28.	All Groups participating in an intergroup study should be able to conduct direct registration	Cancer Trials Support Units will facilitate cross-group registrations. CCOP pilot of direct registrations across adult multi-modality groups is being implemented. An Extended Participation Project

	and submit forms directly to the coordinating Group.	(Attachment 9) which will allow cross-group registrations by new physician participants is underway.
30.	Tissue samples and related clinical data should be stored and maintained by the coordinating Cooperative Group.	This issue will require additional discussion with the Group Chairs. The Cooperative Group experience has shown that a critical factor in the success of tissue banking is the referring pathologist's confidence and trust in the banking pathologist. For this reason, the Groups prefer to keep the collection of samples for Inter- and Intra-Group studies uniform, and within the Group bank where relationships have been nurtured. However for Intergroup studies, the Cooperative Groups have formed disease-specific Correlative Sciences Committees charged with providing peer review for requests for the use of specimens from Intergroup studies. In addition, an Intergroup Specimen Banking Committee has been initiated to coordinate issues such as quality control, informed consent, and informatics specifically related to Intergroup studies. These Committees should help to assure that high quality correlative science is performed on specimens from major Intergroup studies.

VIII. Development: Facilitating the development steps necessary to convert interesting molecules (or physicochemical insights into drugs (or devices) suitable for clinical testing

The RAID Project was developed in order to assist extramural investigators with the transition from preclinical studies through "proof of principle" early clinical trials. It is described in Attachment 5.

IX. Strengthening Partnerships/ Strengthening Industry Relations

- **What kind of partnerships are desirable?**
- **Are any important partners missing**
  - **payers and health-care delivery organizations**
  - **cancer advocacy groups**
  - **pharmaceutical, biotechnology, device, and informatics companies**
  - **Food and Drug Administration**
  - **minority participant organizations (NMA)**

The Office of Clinical Research Promotion (ORCP) has been created to address these and other issues. The Office of Clinical Research Promotion is actively engaged in a number of initiatives to assure coverage of patient care costs in clinical trials. These include:

- the management of the clinical trials agreements with the Department of Defense and the Department of Veterans Affairs. NCI will be presenting a proposal to expand the DoD agreement to include phase I and prevention trials at a September meeting with Pentagon staff.
- continued discussions with individual health plans about the benefits of clinical trials and possible demonstrations providing coverage of clinical trials as a benefit.
- working with cancer centers and clinical investigator groups in support of state initiatives to cover cancer clinical trials.
- worked with HCFA staff to develop the administration proposal for a Medicare demonstration for coverage of clinical trials.
- co-chairing a NIH-working group to negotiate a clinical trials agreement with the American Association of Health Plans. NIH has submitted a final proposal that is being reviewed by the AAHP Board in September.
- development of a public-oriented Cancer Trials web site to provide general information about the importance cancer clinical trials. An important component of the site is the news section that provides timely updates about research advances and clinical trials results. An interactive capability allows visitors to the site to receive additional news updates and more specific information about enrollment for new trials.
- communicate new clinical trials results to health plans as part of an education process. For example, an informational mailing about the results of the breast prevention trial was sent to the major health plans.
- serve as a resource for the identification of health plan representatives to participate in appropriate NCI meetings and work groups.
- work with HMO's to expand participation in NCI-sponsored trials. The OCRP staff are working with CTEP to develop agreements with HMO's to participate in the Expanded Participation Project.
- funding economic studies at Kaiser, Group Health and Mayo Clinic and coordinating and funding a multi-institutional study by RAND Corporation to evaluate the incremental costs of clinical trials. Results of these studies will provide much needed information in understanding clinical trials costs.

Initiatives to address the growing number of complex issues which complicate interactions between clinical investigators and the pharmaceutical/biotechnology industries were described. Increasing difficulties negotiating clinical trial agreements and others were raised. The increasing disparity between NCI and industry funding for clinical trials was described as a major obstacle to enrolling patients on NCI clinical trials. NCI has identified a group of industry representatives to work with NCI, investigators, and others on several of the key issues which were identified, including: data reduction, better use of and investment in the clinical trials infrastructure, suitable language for a generic clinical trials agreement.

In addition to Minority Accrual Initiatives which are funded in a number of the Cooperative Groups, CTEP has initiated an informatics initiative, The Physician Communication Module (described in Attachment 11) in

collaboration with Howard University Cancer Center. This project has multiple objectives, including establishing electronic connectivity with physicians in their offices. The goal is to facilitate enrollment of patients on clinical trials from their treatment settings. In the course of this project, culturally sensitive educational materials and other focused projects will be developed. It is hoped that this will stimulate increased participation of minority physicians and patients in clinical trials.

Armitage Recommendation		Implementation Committee Response
11.	The NCI should continue to develop strategies (including necessary data bases) to convince payers that clinical trials are the preferred way to manage patients, that they represent a better standard of care, and ultimately result in decreased costs.	The Office of Clinical Research Promotion has been created to address these and other issues
13.	Representatives of the patient and high-risk communities need to be integrated into the clinical trials decision making process.	As the decision-making process is reconfigured, consumer representatives will be included in it. This inclusion needs to take place at the level of cooperative-group decision-making as well. Most Groups have already moved to assure inclusion of consumers. Concept Review Committees will include patient representatives
32.	The NCI should urge the FDA to form a single oncology advisory committee with provision for obtaining necessary expertise for ad hoc review.	**NCI has communicated this recommendation to the FDA**
33.	The NCI should enlist the clinical trials and patient communities as well as the pharmaceutical industry to work with the FDA to develop uniform standards and reporting requirements for everyone involved in oncology clinical trials (e.g., pharmaceutical industry, academia, Cooperative Groups).	NCI has met with both FDA and industry to initiate the Common Data Elements and Data Reduction initiatives. The initial meeting with pharmaceutical/biotechnology representatives was held in May 1998. This has been an ongoing topic at monthly NCI/FDA meetings. Both Groups are very enthusiastic. Working groups will be formed in 10/98, to include also clinical investigators, statisticians, and patient advocates to establish standards. An initial meeting is envisioned before 1/99.
34.	The NCI should appoint a group to develop legal templates for interactions between universities, Cooperative Groups, and industry for material transfer agreements, clinical cooperative agreements, and Cooperative Research And Development Agreements (CRADA)	Over the last two years NCI has intensified its dialogue with representatives of the pharmaceutical and biotechnology industries, as well as with the investigator community, in an effort to work out viable arrangements for the conduct of clinical research that would preserve both investigator flexibility and the essential interests of companies. The participants in this often very complex relationship - investigators, universities, companies, and the government - find themselves in a threatening tangle of restrictions and legal obligations that often limit flexibility and the timely implementation of studies. NCI agrees that a solution is urgently needed and will continue to work vigorously toward one in close association with representatives of the other interested parties. The development of a template which describes the basic tenets of an acceptable agreement between industry and academia might reduce the complexity, duration and difficulty of these negotiations. Such a generic document should be sensitive to the needs of both the clinical investigator, the institution, and the pharmaceutical sponsor. It should establish reasonable expectations and rules of engagement. Complex interactions should also be addressed, such as those involved when more than one investigational agent is used and the proprietary rights and intellectual property of more than one company are involved. Such a generic agreement would establish ground rules for subsequent negotiations which should benefit all parties and facilitate the conduct of clinical trials. NCI will begin work immediately with a small group to develop a model agreement and to expand these discussions to include university technology transfer

	officials. In addition, over the past 18 months, the Regulatory Affairs Branch of CTEP has developed and refined several legal templates to address a number of the common issues which develop between clinical investigator and pharmaceutical companies involved in NCI sponsored trials. These include the following; • For agents that NCI is co-developing with an industrial partner, the Clinical Trials Agreement (CTA) or Cooperative Research and Development Agreement (CRADA) covers the provision of agent to the NCI for distribution to investigators for mutually approved studies. For studies approved by industry, the investigator and the NCI, there is no need for a separate agreement for these would be within the scope of the NCI agreement with the industry partner. • For agents developed by NCI, not covered by an agreement with industry, a Material Transfer Agreement (MTA) could be used for the transfer of material for preclinical development, and we are developing a Clinical Research Agreement (CRA) that may be appropriate for clinical studies to be carried out independent of funding by the NCI. • NCI is in the process of instituting several changes to our standard agreements which should simplify the interactions of the Groups with industry and abrogate the need of industry to insist on a separate sponsored research agreement for each study. (However, should there be a need for such an agreement, the NCI has worked with industry and some academic institutions to develop a simplified model that does not conflict with the CTA or CRADA provisions.) • Language was recently approved for incorporation into a letter to be sent to all funded institutions covering patent rights that would be applicable to all investigators/institutions carrying out studies with NCI investigational agents. This letter would agree to offer the rights of first refusal for the licensing of any invention to the company which supplied the investigational agent.
Armitage Recommendation	**Implementation Committee Response**
35. The public should have access to all information about ongoing trials (e.g., through PDQ). The only justified situations for undisclosed trials are those which are funded, in total, by private interests.	The redesign of the PDQ System into the Clinical Trials Information System addresses these issues. The recommendations for the redesign are described in detail in Attachment 10. Ten working teams have been established and have already begun working on implementation of the recommendations.
46. Cooperative Groups should be engaged as early as possible in CTEP CRADA negotiations that will require group participation.	Engaging the Cooperative Groups in the CRADA negotiation process would be problematic because much of the material presented or discussed is confidential in nature and might jeopardize and restrict the Groups' ability to freely interact with other companies. All pharmaceutical companies interacting with CTEP do so with the expectation of total confidentiality. The companies often present their total development plan and anticipated time lines. Whenever these plans include specific trials that they would like the Groups to perform, the Groups are brought into the discussions. CTEP would not commit the Groups without their concurrence. In many cases, CTEP encourages the Company to interact directly with the Groups for the details of design, data collection and funding of specific trials. In addition, CTEP now regularly shares with the Group Chairs lists of CRADAs and Clinical Trials Agreements which are ongoing and in negotiation, as well as non-proprietary aspects of the agreements. This improved communication has substantially reduced the level of

	concern associated with these agreements.
38. The Decision Network needs to be publicized and would benefit from external input. CTEP must clarify its role in reviewing novel drugs with questionable patent status to better move these agents towards clinical trials.	The decision-making process for drugs and biologics is currently under active reconsideration and restructuring. A plan for this will be announced in association with NCI's response to the outside review of the Developmental Therapeutics Program. This restructuring will feature involvement of experts external to the NCI as integral participants in the process. Concerning the development of novel agents that have "questionable patent status," there are many examples (e.g., taxol, pentostatin, high-dose methotrexate, interleukin-2) of drugs that would have been neglected except for strong NCI involvement during the early or middle stages of clinical development. NCI will continue to support the development of meritorious agents irrespective of potential market size or commercial interest.
39. The NCI should work with other governmental agencies and private organizations, including third party payers, to determine the actual costs associated with Phase I through IV clinical trials, and should develop a plan for funding research required to determine these costs.	To address the question of the patient care costs of clinical trials, the NCI is funding economic studies at Kaiser of Northern California, Group Health of Puget Sound and Mayo Clinic. These studies have been completed and are being analyzed. A large study is also being co-funded by NCI and the Office of Science and Technology Policy at the White House to look at patient care costs on clinical trials. This study is being conducted by the RAND Corporation with a sample size of 1500 patients (750 on clinical trials and 750 treated off clinical trials). The IC recommended that NCI conduct a study of the incremental costs associated with Phase I trials and that NCI continue its vigorous attempts to secure coverage for all clinical trials, including Phase I trials, by payer organizations

XII. Human Subjects Protection: Optimization of the informed consent process and IRB review

- informed consent
- tissue issues
- OPRR/IRBs

After extensive discussions with OPRR (the Office for Protection from Research Risks) and the FDA, the NCI has developed a pilot project to explore the use of a central Institutional Review Board (IRB) for the review of clinical trials which it sponsors in the CALGB (Cancer and Leukemia Group B). See attachment 16. This central IRB will be run by the NCI and will be comprised of national experts, patients, ethicists and others. It will provide its review of the protocol to participating local IRBs and establish an ongoing interactive relationship with them. The central IRB will keep local IRBs informed of relevant toxicity experience for the trial nationally, at all sites. It will provide feedback regarding protocol adherence at the site as determined on the basis of routine audits. NCI believes that this collaborative relationship with local IRBs will facilitate review at the local sites and allow them to provide better and more complete oversight of the protection of their patients participating in NCI clinical trials.

14. The informed consent process must be greatly modified and simplified. The NCI should work with OPRR to develop a template for informed consent for distribution to clinical scientists and the patient community.	An Informed Consent Working Group composed of physicians, nurses, ethicists, advocates, lawyers and communications experts has been working in consultation with staff from NCI, OPRR and FDA on informed consent issues. They have developed a simplified informed consent template (Attachment 15). The template and instructions and letters from OPRR and NCI will be distributed to 1500 IRBs, Cooperative Groups, cancer centers, Phase I and II investigators in September, 1998. The templates are also available on the CTEP web site and the entire report is available on the Cancer Trials web site. The Director's Consumer Liaison Group will also distribute the templates to cancer advocacy groups.

25. Simplified informed consent documents will assist both trial participants and physicians (see also Section III) and are essential.	See answer to #14 above.

XIII. Informatics: A powerful modern infrastructure for the secure acquisition and transmitting of data

- Optimize data collection through development of common standards, definitions and data elements across the clinical trials program

- Innovative tools to provide relevant information and educational materials about clinical trials to all who need it and to link with excellent databases of other organizations

Information on NCI's extensive informatics initiatives is included in Attachment 11.

Armitage Recommendation	Implementation Committee Response
15. Uniformity in data collection for clinical trials is essential.	The Common Data Elements/Common Case Report Forms informatics initiative has been ongoing for many months and is described in Attachment 11. There have been two meetings of national breast cancer experts representing a variety of disciplines, including surgery, medical oncology, pathology, radiology, biostatistics, and others. Representatives of Cooperative Groups and cancer centers have been active participants, including several Group statisticians who are working to develop common case report forms in breast cancer. The initial data modeling has been completed and the first set of common data elements in breast cancer will be available in 10/98 for further review and refinement. Following adoption of common data elements for breast cancer, other common malignancies will follow over the next 3 months. NCI is also working with the Group statisticians on the development of common case report forms in GI, lung, leukemia and a number of other disease. Much work has already been completed on common elements and forms for endpoints as part of the Expanded Participation Project (Attachment 9).
31. To be able to create and prioritize the best new ideas in cancer treatment and prevention, the NCI-funded cooperative group and cancer centers should be provided with the means to access all relevant electronic databases, and should be primary participants in development and testing of the new NCI informatics system. A single informatics system for the NCI, all cancer centers, and all Cooperative Groups is important to the success of the clinical trials program.	In addition to the efforts described in number 15 above, the Cooperative Groups and cancer centers have been afforded numerous opportunities to participate in NCI's informatics development initiatives. Both have been extensively represented on the external participant groups for CTEP's applications including the Transition Team, Technical Team, Clinical Data Update and Common Toxicity Criteria groups. Both constituencies are represented on the Long-Range Planning Committee for NCI informatics and will be well represented on the Clinical Trials Task Force associated with that committee. Extensive informatics presentations have been made to both Cooperative Group Chairs and Cancer Center Directors to inform them about ongoing initiatives. In addition, CTEP has already provided substantial supplemental funding to each of the Cooperative Groups in accord with their submitted budgets to facilitate modifications to their systems to allow them to utilize CTEP's new electronic data reporting systems. CTEP has also provided on-site training for its informatics applications at all of the Cooperative Groups' spring meetings. All applications are deployed over the Internet and online and telephone HELP lines are available. NCI is committed to developing standards and systems which will result in uniform informatics systems across the clinical trials program.

OTHER ISSUES

TRAINING

NCI's Strategic Plan for Research Training and Career Development is included as attachment 17.

Armitage Recommendation	Implementation Committee Response
1. A patient-oriented clinical cancer research and training study section in the Division of Research Grants is critical for the success of oncology research.	The Clinical Oncology Special Emphasis Panel has been approved and is being empaneled now. It will review grants beginning with the October receipt cycle. Concerning training, the NCI has the authority to review all NRSAs and career development awards EXCEPT the F32, which is of no value in training clinical scientists. Thus, for training and career development awards, there will be review groups that have a patient-oriented perspective.
2. Awards to mid-career and senior scientists should emphasize salary to ensure protected time for them to devote to clinical investigation.	The NCI is in the process of developing a career award mechanism (the K24) that will provide established clinical scientists 50% salary support as protected time to conduct research or engage in any activities directly related to research (e.g., mentoring).
3. Clinical investigator salary lines should be made available on cancer center's core grants. These salary lines should be for a three to five-year duration.	The NCI does not plan to take this course of action specifically for two reasons. First, the CCSG has a staff investigator budget category that can already support clinical researchers who serve a special role for the cancer center. Second, the NCI would rather develop a broader program which is accessible to all clinical researchers whether they reside in cancer centers or in institutions without cancer centers. This will achieve two purposes: broader access by the clinical research community and a more equitable way of managing the peer review process. See below for the NCI's plans to develop specialized career development awards and transition awards.
4. K12 and T32 awards should be expanded and K08 awards should be directed to patient-oriented research. NCI should create new awards for junior faculty and for midcareer salary support.	The T32 mechanism is not a good mechanism for supporting clinical scientists because it is a National Research Service Award that is both limited in time of support to postdocs (3 years) and salary caps that are not attractive alternatives for M.D.s. Rather than expanding the KO8, we plan to make the K12 an investigator-initiated mechanism; this is an institutional award that gives the institution the authority to select candidates as well as maintain their tenure beyond 5 years I if necessary (i.e., the K12 is the T32 equivalent for training clinical scientists) Making the K12 investigator-initiated rather than RFA driven makes it much more accessible to the research community. In addition, NCI has initiated the K23 career development program which is the equivalent of the K08 for individually mentored clinical scientists. The culture of using the K08 for training M.D.s in basic research is pretty well established, so the NCI believes it is better to tailor new programs for training clinical scientists rather than changing programs that have proved successful in their own right. The truly novel activity that NCI has proposed to the NCI Board of Scientific Advisors is the creation of "transition awards" specifically intended to support junior faculty beginning to establish their own research programs. This is packaged in two forms: a renewal K08 for M.D.s in basic science and new K22 for M.D.s in clinical research. All of these plans are contingent on approval of the BSA and the availability of new money in FY99.
Armitage Recommendation	**Implementation Committee Response**
5. The NCI should fund at least 10 fellowship programs (similar to the Johns Hopkins University Institutional Training Program)	We are currently funding 15 K12s. The NCI feels that it cannot dictate to academic institutions that they must create a new degreed program, but it can encourage some form of more formal recognition for completing this kind of training as part of

which provide a formalized academic degree program for clinical scientists.	**the K12 training program.**